

# Moral Standards for Research in Developing Countries

## *From “Reasonable Availability” to “Fair Benefits”*

by THE PARTICIPANTS IN THE 2001 CONFERENCE ON ETHICAL ASPECTS OF RESEARCH IN DEVELOPING COUNTRIES

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Over the last decade, clinical research conducted by sponsors and researchers from developed countries in developing countries has grown very controversial.<sup>1</sup> The perinatal HIV transmission studies that were sponsored by the National Institutes of Health and the Centers for Disease Control and conducted in Southeast Asia and Africa inflamed this controversy and focused it on the standard of care—that is, on whether treatments tested in developing countries should be compared to the treatments provided locally or to the best interventions available anywhere.<sup>2</sup> Since then, this debate has expanded to include concerns about informed consent.

A subject that has received less discussion but is potentially even more important is the requirement that any drugs proven effective in the trial be made available to the host population after the trial.<sup>3</sup> There seems to be general agreement that “reasonable availability” is necessary in order to ensure that the subject population is not exploited.

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The participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, “Moving beyond Reasonable Availability to Fair Benefits for Research in Developing Countries” *Hastings Center Report* 34, no. 3 (2004):

This consensus is mistaken, however. A “fair benefits” framework offers a more reliable and justifiable way to avoid exploitation. In this paper we develop the argument for the fair benefits framework in detail and compare the two approaches in a specific case—the trial of hepatitis A vaccine in Thailand.

### **Current Views on the Reasonable Availability Requirement**

The idea of making interventions reasonably available was emphasized in the *International Ethical Guidelines* issued in 1993 by the Council for International Organizations of Medical Sciences’ (CIOMS), and it was reiterated in the 2002 revision in Guideline 10 and its commentary.

As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing. Exceptions to this general requirement should be justified and agreed to by all concerned parties before the research begins.<sup>4</sup>

Four issues have generated disagreement. First, how strong or explicit should the commitment to provide

the drug or vaccine be at the initiation of the research trial? CIOMS required an explicit, contract-like mechanism, agreed to before the trial, and it assigns this responsibility to the sponsors of research. The Declaration of Helsinki's 2000 revision endorses a less stringent guarantee that does not require availability of interventions to be "ensured" "in advance."<sup>5</sup> Several other ethical guidelines suggest "discussion in advance" but do not require formal, prior agreements.<sup>6</sup> Conversely, some commentators insist that the CIOMS guarantee is "not strong or specific enough."<sup>7</sup> For instance, the chair and executive director of the U.S. National Bioethics Advisory Commission (NBAC) contended:

If the intervention being tested is not likely to be affordable in the host country or if the health care infrastructure cannot support its proper distribution and use, it is unethical to ask persons in that country to participate in the research, since they will not enjoy any of its potential benefits.<sup>8</sup>

To address these concerns, others advocate that research in developing countries ethically requires a formal and explicit prior agreement that "includes identified funding" and specifies improvements necessary in the "country's health care delivery capabilities."<sup>9</sup>

The second area of disagreement has concerned who is responsible for ensuring reasonable availability. Are sponsors responsible, as the original CIOMS guideline called for? Does responsibility rest with host country governments? Or international aid organizations? The third area of disagreement focuses on what it means for drugs to be made reasonable available. Does it require that the drug or vaccine be free, subsidized, or at market prices?

Finally, to whom should interventions be made reasonably available? Should they be restricted to participants in the research study? Should they include the village or tribe from

which individual participants were enrolled? Or the whole country in which the research was conducted?

### **The Justification of Reasonable Availability**

Why is reasonable availability thought to be a requirement for ethical research in developing countries? Research uses participants to develop generalizable knowledge that can improve health and health care for others.<sup>10</sup> The potential for exploitation of individual participants enrolled in research as well as communities that support and bear the burdens of research is inherent in every research trial. Historically, favorable risk-benefit ratios, informed consent, and respect for enrolled participants have been the primary mechanisms for minimizing the potential exploitation of individual research participants.<sup>11</sup> In developed countries, exploitation of populations has been a less significant concern because there is a process, albeit an imperfect one, for ensuring that interventions proven effective through clinical research are introduced into the health care system and benefit the general population.<sup>12</sup> In contrast, the potential for exploitation is acute in research trials in developing countries. Target populations may lack access to regular health care, political power, and an understanding of research. Hence, they may be exposed to the risks of research with few tangible benefits. The benefits of research—access to new effective drugs and vaccines—may be predominantly for people in developed countries with profits to the pharmaceutical industry. Many consider this scenario the quintessential case of exploitation.<sup>13</sup>

Supporters deem that reasonable availability is necessary to prevent such exploitation of communities. As one group of commentators put it:

[I]n order for research to be ethically conducted [in a developing country] it must offer the poten-

tial of actual benefit to the inhabitants of that developing country. . . . [F]or underdeveloped communities to derive potential benefit from research, they must have access to the *fruits* of such research.<sup>14</sup> (emphasis added)

Or as the commentary to the 2002 CIOMS Guideline 10 put it:

[I]f the knowledge gained from the research in such a country [with limited resources] is used primarily for the benefit of populations that can afford the tested product, the research may rightly be characterized as exploitative and, therefore, unethical.<sup>15</sup>

### **What Is Exploitation?**

Even though it seems initially plausible, there are a number of problems with making reasonable availability a necessary ethical requirement for multinational research in developing countries. The most important problem is that the reasonable availability requirement embodies a mistaken conception of exploitation and therefore offers wrong solution to the problem of exploitation.

There are numerous ways of harming other individuals, only one of which is exploitation. Oppression, coercion, assault, deception, betrayal, and discrimination are all distinct ways of harming people. They are frequently all conflated and confused with exploitation.<sup>16</sup> One reason for distinguishing these different wrongs is that they require very different remedies. Addressing coercion requires removing threats, and addressing deception requires full disclosure, yet removing threats and requiring full disclosure will not necessarily prevent exploitation.

What is exploitation? In the useful analysis developed by Alan Wertheimer, Party A exploits party B when B receives an unfair level of benefits as a result of B's interactions with A.<sup>17</sup> Whether B's benefits are fair depends upon the burdens that B

bears as part of the interaction and the benefits that A and others receive as a result of B's participation in the interaction. If B runs his car into a snow bank and A offers to tow him out but only at the cost of \$200—when the normal and fair price for the tow is \$75—then A exploits B.

Wertheimer's conception of exploitation is distinct from the conventional idea that exploitation entails the "use" of someone else for one's own benefit. There are many problems with this familiar conception. Most importantly, if exploitation is made to depend only on instrumental use of another person, then almost all human interactions are exploitative. We constantly and necessarily use other people.<sup>18</sup> In the example above, not only does A exploit B, but B also exploits A, because B uses A to get his car out of the snow bank. Sometimes the word "exploit" refers to a *neutral* use—as when we say that a person exploited the minerals or his own strength. However, in discussions of research, especially but not exclusively when the research occurs in developing countries, exploitation is never neutral; it is always a moral wrong. Consequently, we do not need to mark out all cases of use. We need only to identify those that are morally problematic.<sup>19</sup>

The Wertheimerian conception of exploitation also departs from the commonly cited Kantian conception. As Allan Buchanan characterizes the Kantian conception, "To exploit a person involves the *harmful, merely instrumental utilization* of him or his capacities, for one's own advantage or for the sake of one's own ends."<sup>20</sup> The Kantian conception of exploitation seems to expand beyond use to include a separate harm. But in the case of exploitation, what is this "other harm"? For a Kantian, *to exploit* must mean to use in a way that the other person could not consent to, a way that undermines their autonomy.<sup>21</sup> However in many cases, people consent—with full knowledge and without threats—and yet we think they

are exploited. People in developing countries could consent to being on a research study after full informed consent and still be exploited. Similarly, snow bank-bound B seems exploited even if he consents to being towed out for \$200. Thus the Kantian conception seems mistaken in fusing exploitation with inadequate consent.

In any event, the reasonable availability requirement is not grounded in Kantian claims about use and violation of autonomy. Rather, it is aimed at ensuring that people have access to the interventions that they helped to demonstrate were effective. It is related to the benefits people receive from participating in a research study, not to their autonomy in consent. Consequently, whatever the merits of the Kantian conception of exploitation, it seems irrelevant to deciding whether making the trial intervention reasonably available can prevent exploitation. In contrast, the Wertheimerian view, which locates the core moral issue inherent in exploitation in the fair level of benefits each party of an interaction receives, captures the ethical concern underlying the reasonable availability requirement.

In determining whether exploitation has occurred in any case, the Wertheimerian conception gives us at least six important considerations to bear in mind. First, exploitation is a micro-level concern. Exploitation is about harms from discrete interactions, rather than about the larger social justice of the distribution of background rights and resources. Certainly macro-level distributions of resources can influence exploitation, but the actual exploitation is distinct. Furthermore, while past events may lead people to feel and claim that they have been exploited, whether exploitation occurred does not depend either on their feelings or on historical injustices. Exploitation is about the fairness of an individual exchange. Indeed, as we shall note below, exploitation can happen even in a just society, and it can fail to

occur even when there is gross inequality between the parties. As Wertheimer argues:

[W]hile the background conditions shape our existence, the primary experiences occur at the micro level. Exploitation matters to people. People who can accept an unjust set of aggregate resources with considerable equanimity will recoil when they feel exploited in an individual or local transaction. . . . Furthermore, micro-level exploitation is not as closely linked to macro-level injustice as might be thought. Even in a reasonably just society, people will find themselves in situations [that] will give rise to allegations of exploitation.<sup>22</sup>

The reasonable availability requirement recognizes the possibility of exploitation associated with a particular study, and it does not require ensuring the just distribution of all rights and resources or a just international social order. This is more than just a pragmatic point; it reflects the deep experience that exploitation is transactional.

Second, because exploitation is about interactions at a micro level, between researcher and community, it can occur only once an interaction is initiated. In this sense, the obligations to avoid exploitation are obligations that coexist with initiating an interaction.

Third, exploitation is about "how much," not "what," each party receives. The key issue is fairness in the level of benefits. Moreover, exploitation depends upon fairness, not "equalness." An unequal distribution of benefits may be fair if there are differences in the burdens and contributions of each party. Fairness in the distribution of benefits is common to both Wertheimer's theory of exploitation and Rawls's theory of justice, but the notion of fairness important for exploitation is not Rawlsian. They differ in that Rawls addresses macro- and Wertheimer micro-level distributions of benefits. The Rawlsian conception of fairness addresses the dis-

tribution of rights, liberties, and resources for the basic structure of society within which individual transactions occur.<sup>23</sup> In other words, Rawlsian fairness is about constitutional arrangements, taxes, and opportunities. Rawls's conception has often but wrongly been applied to micro level decisions, where it usually issues in implausible and indefensible recommendations. Fairness in individual interactions, which is the concern of exploitation, is based on ideal market transactions.<sup>24</sup> Thus a fair distribution of benefits at the micro-level is based on the level of benefits that would occur in a market transaction devoid of fraud, deception, or force, in which the parties have full information. While this is always idealized—in just the way that economic theory is idealized—it is the powerful ideal informing the notion of fairness of micro-level transactions. This notion of fairness is also relative: just as fair price in a market is based on comparability, so too is the determination of fair benefits based on comparisons to the level of benefits received by other parties interacting in similar circumstances.

Fourth, that one party is vulnerable may make exploitation more likely, but does not inherently entail exploitation. Since exploitation involves the distribution of benefits and burdens, vulnerability is neither necessary nor sufficient for its occurrence. The status of the parties is irrelevant in determining whether exploitation has occurred. If the exchange is fair to both parties, then no one is exploited, regardless of whether one party is poor, uneducated, or otherwise vulnerable and disadvantaged. In the case of snow-bound B, if A charges B \$75 for towing the car out, then B is not exploited even though B is vulnerable.

Fifth, since exploitation is about the fairness of micro-level interactions, the key question is the level of benefits provided to the parties *who interact*. Determining whether exploitation has occurred does not involve weighing the benefits received

by people who do not participate in the interaction.

Finally, because fairness depends on idealized market transactions, determining when exploitation occurs—when the level of benefits is unfair—will require interpretation. As with the application of legal principles and constitutional provisions, the inevitability of interpretation means that reasonable people can and will disagree. But such interpretation and controversy does not invalidate either judicial or moral judgments.

### Problems with the Reasonable Availability Requirement

The fundamental problem with the reasonable availability standard is that it guarantees a benefit—the proven intervention—but not a *fair level* of benefits, and therefore it does not necessarily prevent exploitation. Reasonable availability focuses on *what*—the products of research—but exploitation requires addressing *how much*—the level of benefit. For some research in which either the subjects would be exposed to great risks or the sponsor stands to gain enormously, reasonable availability might be inadequate and unfair. Conversely, for very low- or no-risk research in which the population would obtain other benefits, or in which the benefits to the sponsor are minimal, requiring the sponsor to make a product reasonably available could be excessive and unfair.

There are also other problems with the reasonable availability standard. First, it embodies a very narrow notion of benefits. It suggests that only one type of benefit—a proven intervention—can justify participation in clinical research. But a population in a developing country could consider a diverse range of other benefits from research, including the training of health care or research personnel, the construction of health care facilities and other physical infrastructure, and the provision of public health measures and health services beyond those required as part of the

research trial. The reasonable availability standard ignores such benefits, and hence cannot reliably determine when exploitation has occurred.

Second, at least as originally formulated by CIOMS, the reasonable availability standard applies to only a narrow range of clinical research—successful Phase III testing of interventions.<sup>25</sup> It does not apply to Phase I and II drug and vaccine testing, or to genetic, epidemiology, and natural history research, which are all necessary and common types of research in developing countries but may be conducted years or decades before any intervention is proven safe and effective. Consequently, either the reasonable availability requirement suggests that Phase I and II studies cannot be ethically conducted in developing countries—a position articulated in the original CIOMS guidelines but widely repudiated—or there is no ethical requirement to provide benefits to the population when conducting such early phase research, or reasonable availability is not the only way to provide benefits from a clinical research study.

To address this gap, CIOMS altered the reasonable availability requirement in 2002:

Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that. . . any intervention or product developed, or *knowledge generated*, will be made reasonably available for the benefit of that population or community.<sup>26</sup> (emphasis added)

According to CIOMS some knowledge alone may constitute a fair level of benefits for some non-Phase III studies. But in many non-Phase III studies, it may not match either the risks to subjects or the benefits to others. Indeed, the requirement could permit pharmaceutically sponsored Phase I and II testing of drugs in developing countries while shifting Phase III testing and sales to developed countries as long as data from

the early studies are provided to the developing countries. This modification to encompass non-Phase III studies might actually invite *more* exploitation of developing countries.

Third, even in Phase III studies, the reasonable availability requirement provides an *uncertain* benefit to the population, since it makes benefit depend on whether the trial is a “successful testing” of a new product. If there is true clinical equipoise at the beginning of Phase III trials conducted in developing countries, then the new intervention should be proven more effective in only about half of the trials.<sup>27</sup> Consequently, reliance on reasonable availability alone to provide benefits implies that the host country will receive sufficient benefits from half or fewer of all Phase III studies.

Fourth, assuring reasonable availability does not avert the potential for undue inducement of a deprived population. One worry about research in developing countries is that collateral benefits will be escalated to induce the population to enroll in excessively risky research. If the population lacks access to public health measures, routine vaccines, medications for common ailments, and even trained health care personnel, then providing these services as part of a research study might induce them to consent to the project despite its risks, and despite the fact that it disproportionately benefits people in developed countries.<sup>28</sup> Similarly, guaranteeing reasonable availability to a safe and effective drug or vaccine after a study could also function as an undue inducement if the population lacks basic health care.

Fifth, it is beyond the authority of researchers and even of many sponsors of research to guarantee reasonable availability. Clinical researchers and even some sponsors in developed countries, such as the NIH and Medical Research Council, do not control drug approval processes in their own countries, much less in other countries. Similarly they do not control budgets for health ministries or for-

eign aid to implement research results, and may be, by law, prevented from providing assistance with implementation of research results. At best, they can generate data to inform the deliberations of ministers of health, aid officials, international funding organizations, and relevant others, and then try to persuade those parties to implement effective interventions.

Further, because most Phase III trials take years to conduct, policymakers in developing countries and aid agencies may resist agreements to provide an intervention before they know how beneficial it is, the logistical requirements for implementing and distributing it, and how it compares to other potential interventions. Such cautiousness seems reasonable given the scarce resources available for health delivery.

Sixth, requiring reasonable availability tacitly suggests that the population cannot make its own, autonomous decisions about what benefits are worth the risks of a research trial. In many cases the resources expended on making a drug or vaccine available could be directed to other benefits instead, which the host community might actually prefer. Disregarding the community's view about what constitutes appropriate benefits for them—insisting that a population must benefit in a specific manner—implies a kind of paternalism.

Finally, requiring a prior agreement to supply a proven product at the end of a successful trial can become a “golden handcuff,” constraining rather than benefiting the population. If there is a prior agreement to receive a specific drug or vaccine, rather than cash or some other transferable commodity, the prior agreement commits the population to using the specific intervention tested in the trial. (Pharmaceutical companies are likely to provide their own product directly and avoid agreements in which they are required to provide the product of a competitor.) Yet if other, more effective or desirable interventions are developed, the population is unlikely to have the re-

sources to obtain those interventions. Hence prior agreements can actually limit access of the population to appropriate interventions.

Because of these difficulties, the reasonable availability requirement is recognized more in the breach than in its fulfillment; consequently much effort has been devoted to identifying and justifying exceptions.

## The Fair Benefits Framework

Certainly, targeted populations in developing countries ought to benefit when clinical research is performed in their communities. Making the results of the research available is one way to provide benefits to a population, but it is not the only way. Hence it is not a necessary condition for ethical research in developing countries, and it should not be imposed unless the developing countries have themselves affirmed it.

This was the consensus of the clinical researchers, bioethicists, and IRB chairs and members from eight African and three Western countries—Egypt, Ghana, Kenya, Malawi, Mali, Nigeria, Tanzania, Uganda, Norway, the United Kingdom, and the United States—who participated in the 2001 Conference on Ethical Aspects of Research in Developing Countries (EARD). (See the attached list.) As an alternative to reasonable availability, this group proposes the “fair benefits framework.”<sup>29</sup>

The fair benefits framework supplements the usual conditions for the ethical conduct of research trials, such as independent review by an institutional review board or research ethics committee and individual informed consent.<sup>30</sup> In particular, it relies on three background principles that are widely accepted as requirements for ethical research. First, the research should have social value: it should address a health problem of the developing country population. Second, the subjects should be selected fairly: the scientific objectives of the research itself, not poverty or vulnerability, must provide a strong jus-

tification for conducting the research in a specific population. The subjects might be selected, for example, because the population has a high incidence of the disease being studied or of the transmission rates of infection necessary to evaluate a vaccine. Third, the research must have a favorable risk-benefit ratio: benefits to participants must outweigh the risks, or the net risks must be acceptably low.

To these widely accepted principles, the fair benefits framework adds three further principles, which are specified by fourteen benchmarks (see the table):

**Principle 1: Fair Benefits.** There should be a comprehensive delineation of tangible benefits to the research participants and the population from both the conduct and results of the research. These benefits can be of three types: (1) benefits to research participants during the research; (2) benefits to the population during the research; or (3) benefits to the participants and population after completion of the research. It is not necessary to provide each of these types of benefits; the ethical imperative based on the conception of exploitation is only for a fair level of benefits. It would seem fair that as the burdens and risks of the research increase, the benefits should also increase. Similarly, as the benefits to the sponsors, researchers, and others outside the population increase, the benefits to the host population should also increase.

Because the aim of the fair benefits framework is to avoid exploitation, the population at risk for exploitation is the relevant group to receive benefits and determine their fairness. Indeed, determination of whether the distribution of benefits is fair depends on the level of benefits received by those members of the community who actually participate in the research, for it is they who bear the burdens of the interaction. However, each benefit does not have to accrue solely to the research participants; a benefit could be directed in-

**TABLE 1: The Fair Benefits Framework**

<i>Principles</i>	<b>Benchmarks for determining whether the principle is honored.</b>
<i>Fair benefits</i>	<ul style="list-style-type: none"> <li>• <b>Benefits to participants during the research</b> <ol style="list-style-type: none"> <li><b>1) Health improvement:</b> Health services that are essential to the conduct of the research will improve the health of the participants.</li> <li><b>2) Collateral health services:</b> Health services beyond those essential to the conduct of the research are provided to the participants.</li> </ol> </li> <li>• <b>Benefits to participants and population during the research</b> <ol style="list-style-type: none"> <li><b>3) Collateral health services:</b> Additional health care services are provided to the population.</li> <li><b>4) Public Health Measures:</b> There are additional public health measures provided to the population.</li> <li><b>5) Employment and economic activity:</b> The research project provides jobs for the local population and stimulates the local economy.</li> </ol> </li> <li>• <b>Benefits to population after the research</b> <ol style="list-style-type: none"> <li><b>6) Availability of the intervention:</b> If proven effective, the intervention should be made available to the population.</li> <li><b>7) Capacity development:</b> There are improvements in health care physical infrastructure, training of health care and research personnel, or training of health personnel in research ethics.</li> <li><b>8) Public health measures:</b> Additional public health measures provided to the population will have a lasting benefit.[OK?]</li> <li><b>9) Long-term collaboration:</b> The particular research trial is part of a long-term research collaboration with the population.</li> <li><b>10) Financial rewards:</b> There is a plan to share fairly with the population the financial rewards or intellectual property rights related to the intervention being evaluated.</li> </ol> </li> </ul>
<i>Collaborative partnership</i>	<ol style="list-style-type: none"> <li><b>1) Free, uncoerced decisionmaking:</b> The population is capable of making a free, uncoerced decision: it can refuse participation in the research.</li> <li><b>2) Population support:</b> When it has understood the nature of the research trial, the risks and benefits to individual subjects, and the benefits to the population, the population decides that it wants the research to proceed.</li> </ol>
<i>Transparency</i>	<ol style="list-style-type: none"> <li><b>1) Central repository of benefits agreements:</b> An independent body creates a publicly accessible repository of all formal and informal benefits agreements.</li> <li><b>2) Community consultation:</b> Forums with populations that may be invited to participate in research, informing them about previous benefits agreements.</li> </ol>

stead to the entire community. For instance, capacity development or enhanced training in ethics review would be provided to the community, and then benefit the participants indirectly. The important question is how much the participants will benefit from these measures.

In addition, the community will likely bear some burdens and impositions of the research because its health care personnel are recruited to staff the research teams, and its physical facilities and social networks are utilized to conduct the study. Thus, to avoid exploitation, consideration of the benefits for the larger community may also be required. However, since exploitation is a characteristic of micro-level transactions, there is no justification for including everybody in an entire region or country in the distribution of benefits (nor in the decisionmaking that is required by the next principle) unless the whole region or country is involved in bearing the burdens of the research and at risk for exploitation.

**Principle 2: Collaborative Partnership.** The population being asked to enroll determines whether a particular array of benefits is sufficient and fair. Currently, there is no shared international standard of fairness; reasonable people disagree.<sup>31</sup> More importantly, only the host population can determine the value of the benefits for itself. Outsiders are likely to be poorly informed about the health, social, and economic context in which the research is being conducted, and they are unlikely to fully appreciate the importance of the proposed benefits to the population.

Furthermore, the population's choice to participate must be free and uncoerced; refusing to participate in the research study must be a realistic option. While there can be controversy about who speaks for the population being asked to enroll, this is a problem that is not unique to the fair benefits framework. Even—or especially—in democratic processes, unanimity of decisions cannot be the standard; disagreement is inherent.

But how consensus is determined in the absence of an electoral process is a complex question in democratic theory beyond the scope of this article.

**Principle 3: Transparency.** Fairness is relative, since it is determined by comparisons with similar interactions. Therefore transparency—like the full information requirement for ideal market transactions—allows comparisons with similar transactions. A population in a developing country is likely to be at a distinct disadvantage relative to the sponsors from the developed country in determining whether a proposed level of benefits is fair. To address these concerns, a publicly accessible repository of all benefits agreements should be established and operated by an independent body, such as the World Health Organization. A central repository permits independent assessment of the fairness of benefits agreements by populations, researchers, governments, and others, such as nongovernmental organizations. There could also be a series of community consultations to make populations in developing countries aware of the terms of the agreements reached in other research projects. Such information will facilitate the development of “case law” standards of fairness that evolve out of a number of agreements.

Together with the three background conditions, these three new principles of the fair benefits framework ensure that: (1) the population has been selected for good scientific reasons, (2) the research poses few net risks to the research participants, (3) there are sufficient benefits to the participants and population, (4) the population is not subject to a coercive choice, (5) the population freely determines whether to participate and whether the level of benefits is fair given the risks of the research, and (6) there is an opportunity for comparative assessments of the fairness of the benefit agreements.

## Application to the Hepatitis A Vaccine Case

We can compare the reasonable availability requirement with the fair benefits framework in the case of Havrix, an inactivated hepatitis A vaccine that was tested in 1990 among school children from Kamphaeng Phet province in northern Thailand.<sup>32</sup> The study was a collaboration of the Walter Reed Army Institute of Research (in the United States), SmithKline Beecham Biologicals, and Thailand's Ministry of Public Health. Initially, there was a randomized, double-blind Phase II study involving 300 children, primarily family members of physicians and nurses at the Kamphaeng Phet provincial hospital. After a demonstration of safety and of an antibody response that neutralizes hepatitis A, a randomized, double blind Phase III study with a hepatitis B vaccine control involving 40,000 children, one to sixteen years old, was initiated to assess protection against hepatitis A infection.

The study was conducted in Thailand for several reasons. First, there were increasingly common episodes of hepatitis A infection during adolescence and adulthood, including hepatitis A outbreaks, such as at the National Police Academy in 1988. Second, while hepatitis A transmission was focal, there was a sufficiently high transmission rate—119 per 100,000 population—in rural areas to assess vaccine efficacy. Third, the area had been the site of a prior Japanese encephalitis vaccine study.<sup>33</sup> Ultimately, the Japanese encephalitis vaccine was registered in Thailand in 1988 and included in the Thai mandatory immunization policy in 1992.

Prior to the Phase III study, there was no formal agreement to make Havrix widely available in Thailand. Due to competing vaccination priorities (especially for implementation of hepatitis B vaccine), the cost of a newly developed hepatitis A vaccine, and the available health care budget

in Thailand, it was unlikely that Havrix would be included in the foreseeable future in Thailand's national immunization program, in which vaccines are provided to the population at no cost. In addition, SmithKline Beecham Biologicals made no commitment to provide free Havrix to Thailand. However, proven the company did commit to provide the vaccine to all research participants effective and to pursue Havrix registration in Thailand, enabling the vaccine to be sold in the private market. While there was no promise about what the prices would be for the private market, SmithKline Beecham Biologicals had previously utilized tiered pricing on vaccines. Registration and distribution would enable the Ministry of Public Health to use Havrix to control hepatitis A outbreaks at schools and other institutions. Nevertheless, at the start of the trial, all collaborators recognized that the largest market for Havrix would be travelers from developed countries.

Was the Havrix study ethical? Although all the study participants ultimately received hepatitis A and B vaccines, the study did not fulfill the reasonable availability requirement. There was no prior agreement to provide the vaccine to everyone in Kamphaeng Phet province, and since most Thais would not be able to afford the vaccine, committing to registering and selling it on the private market does not seem to "reasonably available." Thus, by this standard, the trial seems to be unethical.

The fair benefits framework, however, requires a more multifaceted assessment. First, the study seemed to fulfill the background requirements of social value, fair subject selection, and favorable risk-benefit ratio. Hepatitis A was a significant health problem in northern Thailand and recognized as such by the Thai Ministry of Public Health. Although the population in Kamphaeng Phet province was poor, the epidemiology of hepatitis A provided an independent scientific rationale for site selec-

tion. The preliminary data indicated that the candidate vaccine had an excellent safety profile and probable protective efficacy, suggesting a highly favorable risk-benefit ratio for participants.

The benefits of the Havrix trial were of several sorts. By design, all 40,000 children in the trial received both hepatitis A and B vaccines. In addition, regional medical services were augmented. The research team contracted with the community public health workers to examine all enrolled children absent from school at their homes, to provide necessary care, and, if appropriate, to arrange transfer to the district or provincial hospital.

There were also benefits for the provincial population. Public health stations throughout Kamphaeng Phet province that lacked adequate refrigeration to store vaccines, medicines, and blood specimens received new refrigerators. Similarly, rural health stations lacking reliable access to the existing FM wireless network link with the provincial hospital's consultants were joined to the network. In the six schools that had hepatitis A outbreaks during the study, the research team arranged for inspection of the schools and identification of deficiencies in toilet, hand-washing facilities, and water storage contributing to the outbreak. At each school, the researchers contracted and paid to have recommended improvements implemented. In addition, public health workers were provided with unlimited stocks of disposable syringes and needles, as well as training on measures to reduce the incidence of blood-borne diseases. Hepatitis B vaccinations were provided to all interested government personnel working on the trial, including approximately 2,500 teachers, public health workers, nurses, technicians, and physicians. Since deaths of enrolled research participants were tracked and investigated, the research team identified motor vehicle accidents, especially pedestrians struck by cars, as a major cause of mortality in

the province and recommended corrective measures.<sup>34</sup> Finally, the training of Thai researchers and experience in conducting the Havrix trial may have facilitated subsequent research trials, including the current HIV vaccine trials in Thailand.

Regarding the principle of collaborative partnership, there were extensive consultations in Kamphaeng Phet province prior to initiating and conducting the trial. The provincial governor, medical officer, education secretary, and hospital director provided comments before granting their approval. In each of the 146 participating communities, researchers made public presentations about the study and held briefings for interested parents and teachers. Each school appointed a teacher to maintain a liaison with the research team. Parental and community support appeared to be related to the provision of hepatitis B vaccine to all participants, since hepatitis was seen as a major health problem and the children lacked access to the vaccine.

Furthermore, the protocol was reviewed by the Thai Ministry of Public Health's National Ethical Review Committee, as well as by two IRBs in the United States. The Ministry of Public Health appointed an independent committee composed of thirteen senior physicians and ministry officials to monitor the safety and efficacy of the trial. And rejecting the trial appeared to be a genuine option; certainly those Thai scientists who tried hard to prevent it, including by lobbying the National Ethics Review Committee, seemed to think so.

At the time of this trial, there was no central repository of benefits agreements to fulfill the transparency principle. However, the measures taken to benefit the population, including provision of the hepatitis A and B vaccines and registration of Havrix in Thailand, were discussed with the Ministry of Public Health and provincial officials and published.

Did the Havrix study provide fair benefits? Clearly some in Thailand

thought not. They argued that the trial did not address a pressing health need in a manner appropriate to the country; instead, they held, it addressed a health interest of the U.S. army. Second, some have alleged there was insufficient technology transfer. In particular, no training was provided to Thai researchers to conduct testing for the antibody to hepatitis A or to develop other laboratory skills. Third, it was claimed that inadequate respect was accorded to the Thai researchers, as none were among the study's principal investigators and none were named in the original protocol (they were simply referred to as "Thai researchers"). Only after protests were they individually identified. The American investigators claim vehemently that this charge is inaccurate. A prominent vaccine researcher summarized the sentiment against Thai participation:

Journalists in the country have accused the government and medical community of a national betrayal in allowing Thai children to be exploited. . . . The role of Thailand in rounding up its children for immunization was hardly seen as a meaningful partnership in this research aim. In private, government ministers agreed with this, but the

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sway of international politics and money was too persuasive.<sup>35</sup>

Many others argued that the benefits to the population of Kamphaeng Phet province were sufficient, especially given the minimal risk of the study. Still others are uncertain. In their view, the level of benefits were not clearly inadequate, but more long-term benefits could have been provided to the community depending on the level of the sponsors' benefits—in this case, SmithKline Beecham's profits from vaccine sales. To address the uncertainty of how much a company might benefit from drug or vaccine sales, some propose profit-sharing agreements that provide benefits to the community related to the actual profits.

Universal agreement is a naïve and unrealistic goal. The goal is only a consensus in the population to be enrolled in the trial. Consensus on the appropriateness of a research study acknowledges that some disagreement is not only possible but likely, and even a sign of a healthy partnership.<sup>36</sup> In this trial, the national ministry, the provincial governmental and health officials, and the Kamphaeng Phet population seemed supportive.

Further, the dissent focused not on whether the vaccine would be made available to the population if it were proven effective, but on the level of a broad range of burdens and benefits, both to the community and to the sponsors. It is precisely this sort of broad, nuanced, and realistic assessment of the community's interests that is permitted and promoted by the fair benefits framework. Rather than making any one type of benefit into a moral litmus test, the fair benefits framework takes into account all of the various ways the community might benefit from the research.

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